Rabbie R, Derry S, et al. Ibuprofen with or without an antiemetic for acute migraine headaches in adults (Review). Cochrane Database of Systematic Reviews 2010, Issue 10, Art # CD008039.

Design: Meta-analysis of randomized clinical trials

PICOS:

- Patient population: Adults with migraine with or without aura defined by International Headache Society criteria
- Intervention: Self-administered single dose of ibuprofen taken to treat a migraine headache when pain was of moderate or severe intensity; studies of ibuprofen plus an antiemetic were included, provided that both ibuprofen and the antiemetic were self-administered
- Comparison/control intervention: Placebo by self-administration
- Outcomes: Principal outcomes were measured 2 hours and 24 hours after drug administration; for the 2-hour mark, the major outcome was being pain-free, and the secondary outcome was having pain reduction (headache relief); for the 24-hour mark, the outcomes were sustained pain-free and sustained pain reduction, both of which had to be maintained without use of a second dose of any medication
- Study types: randomized double-blind, placebo-controlled or active-controlled studies with at least 10 participants in each arm, reporting dichotomous (success/failure) data for one of the principal outcomes

Study type and selection:

- Databases searched were MEDLINE, EMBASE, Cochrane CENTRAL, and the Oxford Pain Relief Database through 22 April 2010
- Two authors independently selected studies for inclusion, resolving disagreements through discussion with a third author
- Risk of bias was assessed with a five point scale: being randomized, adequate description of the randomization procedure, being double-blind, adequate description of the double-blinding method, and full accounting for dropouts and withdrawals from the study
- Treatment effects were reported as relative risks (RR) of success, in which RR greater than 1 indicates that ibuprofen is more likely to yield successful treatment of the headache symptoms
    - Numbers needed to treat (NNT) were calculated as the number of patients who would need treatment with ibuprofen in order to produce one successful therapeutic outcome
- Most studies were parallel group trials; when crossover trials were included, the first-period data were used in the analysis

Results:

- 9 studies with 4368 participants met entry criteria; none were considered to have a high risk of bias

- Most studies used a standard oral tablet of ibuprofen, but 2 used soluble oral preparations, which may act more rapidly than oral tablets, and these were considered separately
- For 200 mg ibuprofen vs. placebo, 2 studies with 777 patients provided data on total pain-free response and also for headache relief
    - 20% of ibuprofen patients were pain-free at 2 hours; only 10% of placebo patients were pain-free (RR=2.0)
    - 52% of ibuprofen patients had headache relief at 2 hours; only 37% of placebo patients had headache relief (RR=1.4)
- For 400 mg ibuprofen vs. placebo, 6 studies with 2575 patients provided data for total pain-free response at 2 hours, and 7 studies with 1815 patients provided data for headache relief at 2 hours
    - 26% of ibuprofen patients were pain-free at 2 hours; only 12% of placebo patients were pain free (RR=1.9)
    - 57% of ibuprofen patients were pain free at 2 hours, compared with 25% of placebo patients (RR=2.2)
- Other analyses of different doses of ibuprofen (i.e. 600 mg) also reported superior analgesic effects with ibuprofen than with placebo
- Several subgroup analyses were done; one analysis comparing oral tablet and liquid gel administration of ibuprofen suggested that the liquid preparation was superior to the tablet form in providing headache relief 1 hour after administration; at 2 hours after administration, there was no significant difference between liquid and tabled administration
- Another subgroup analysis suggested that 400 mg of ibuprofen was superior to 200 mg for headache relief at 2 hours
- Migraine-associated symptoms (nausea, vomiting, photophobia, phonophobia) were not consistently reported across studies, but the available data did show a favorable effect of ibuprofen compared to placebo
- Only one study provided data on use of an antiemetic (parenteral metoclopramide); because this was not self-administered, the study data were excluded from the analysis

Authors' conclusions:

- For the preferred outcome of pain-free status at 2 hours and for the outcome of pain relief at 2 hours, ibuprofen is superior to placebo
- The included studies were of good methodological quality, and omissions of some descriptions of randomization method may have been due to space limitations rather than any flaw in methodology
- Ibuprofen is an effective treatment for acute migraine headache, reducing pain, associated symptoms, and functional disability within 2 hours; soluble ibuprofen may act more quickly than standard tablet forms of the drug

Comments:

- Although in all of the included studies, ibuprofen was more effective than placebo, there was heterogeneity between studies as reported in the forest plots

    - E.g., Figure 2 (400 mg ibuprofen vs placebo for 2-hour pain-free response) and Figure 5 (400 mg ibuprofen vs placebo for 2-hour pain relief) both show statistical heterogeneity; some studies have much larger effect sizes than others
    - There is no apparent explanation of the heterogeneity, but studies did differ with respect to baseline headache frequency and associated symptoms, and it is possible that different patient samples had different effectiveness of ibuprofen
- Numbers needed to treat (NNT) are reported for most meta-analyses; however, the interpretation of NNT is not always clear when there are large differences in response to placebo; in general, it is fairly clear that only a few patients need to be treated with ibuprofen in order to experience a benefit
- There was one comparison of ibuprofen with rofecoxib, which is no longer on the US market, and is not relevant to the conclusions of the meta-analysis

Assessment: Adequate meta-analysis for good evidence that a single dose of 200 or 400 mg ibuprofen is superior to placebo for relief of acute migraine